

Appl. Serial No. 09/675, ~~675~~
Amdt. dated Dec. 2, 2003
Reply to Office action of June. 6, 2003

PATENT

AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph at page 33, lines 4-8 with the following amended paragraph:

5 The active ingredieints ingredients may be used to provide controlled release pharmaceutical formulations containing an active ingredient ("controlled release formulations") in which the release of the active ingredient is controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

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Please replace the paragraph at page 27, lines 11-15 with the following amended paragraph:

15 One or more of the following methods are used to prepare the enantiomerically enriched or pure isomers herein. The methods are listed in approximately their order of preference, i.e., one ordinarily should employ stereospecific synthesis from chiral precursors before chromatographic resolution or before spontaneous crystallization.

20 Please replace the paragraph at page 76, lines 24-26 with the following amended paragraph:

25 15. Use of a compound of formula 1 or 2 for the manufacture of a medicament for use to treat or prevent an androgen responsive disease in a subject, or to ameliorate one or more symptoms thereof, e.g., ~~in-a-mmal~~ in a mammal or a human.

Please replace the paragraph at page 79, line 9 through page 80, line 5 with the following amended paragraph:

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Appl. Serial No. 09/675,323
Amdt. dated Dec. 2, 2003
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PATENT

Example 2. Induction of AR-mediated transcriptional activity. Steroid compounds were screened for their ability to induce AR transcriptional activity in the AR-negative PC-3 cell line. The results of the CAT assay were obtained by transient co-transfection of AR plasmid and a reporter plasmid (MMTVCAT) 5 containing the CAT gene linked to the androgen response element (ARE). After transfection, the cells were treated with various DHEA derivatives at 1000, 10, and 0.1 nM. As shown in figure 1, compounds Compounds 0, 4, 5, 6, 8, 10, 13, 15, 16, 18, and 22 had little androgenic activity but they did induce a low level of AR-mediated CAT gene transactivation. AED (compound 21) had about the 10 same capacity as DHT to stimulate AR-mediated CAT gene transcription.

Please replace the paragraph at page 80, lines 6-16 with the following amended paragraph:

15 **Example 3. Identification of anti-adiol activity of steroids with low androgenic effects.** Several compounds were screened for their capacity to modulate AED's effects on AR-mediated activation of gene transcription in PC-3 cells. The chemical structures of compounds 4, 6, 8 and 10 are shown in figure 2A. Example 1 above. The PC-3 cells were co-transfected with pSG5 and the 20 MMTV-CAT reporter vector in the presence of 50 nM AED and each compound at a concentration of 10, 100, or 1000 nM. As shown in figure 2B, compounds Compounds 4, 6, 8 and 10 antagonized AED-mediated AR transcriptional activity. At concentrations of 0.1 μ M and 1 μ M, compounds 4 and 6 suppressed the AED-induced AR transactivation to less than 30%. Compounds 0, 5, 13, 15, 25 18 and 22 show either activation of AED-mediated AR transcriptional activity or they have no effect.

Please replace the paragraph at page 80, lines 17-22 with the following amended paragraph:

Appl. Serial No. 09/675,320
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PATENT

Example 4. Identification of anti-DHT effects of steroids. Compounds 4, 6, 8 and 10 were examined to determine whether these AED antagonists had the ability to repress DHT-induced AR transactivation. PC-3 cells were co-transfected with pSG5 and the MMTV-CAT reporter plasmid in the presence 5 of 1 nM DHT and each compound at 10, 100, or 1000 nM. Compound 4 repressed the DHT-induced AR transactivation to less than 40% at 1 μ M (figure 3).

Please replace the paragraph at page 80, lines 23-31 with the following
10 amended paragraph:

Example 5. Suppression of the AED-induced AR transcriptional activity in the presence of HF. To mimic the *in vivo* condition of total androgen blockage in prostate cancer patients, compounds 4, 6, 8 and 10 were examined 15 for their capacity to antagonize AED-induced AR transactivation in the presence of HF. In the presence of 1 μ M HF, 50 nM AED, and each compound at 0.01, 0.1 or 1 μ M, PC-3 cells were transiently transfected with pSG5 and the MMTV-CAT reporter plasmid. ~~As shown in figure 4, HF suppressed AED-mediated AR transcription activity by about 40%. The compounds tested decreased~~
20 AED-mediated AR transcription activity by about 75%.